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NEWS	4	May 12	Polymer links for the POLYLINK command completed in REGISTRY
NEWS	5	May 27	New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus
NEWS	6	May 27	CAplus super roles and document types searchable in REGISTRY
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NEWS	11	AUG 02	IFIPAT/IFIUDB/IFICDB reloaded with new search and display fields
NEWS	12	AUG 02	CAplus and CA patent records enhanced with European and Japan Patent Office Classifications
NEWS	13	AUG 02	STN User Update to be held August 22 in conjunction with the 228th ACS National Meeting
NEWS	14	AUG 02	The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available

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FILE 'HOME' ENTERED AT 20:04:28 ON 02 AUG 2004

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=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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STRUCTURE FILE UPDATES:    1 AUG 2004  HIGHEST RN 720662-84-0
DICTIONARY FILE UPDATES:   1 AUG 2004  HIGHEST RN 720662-84-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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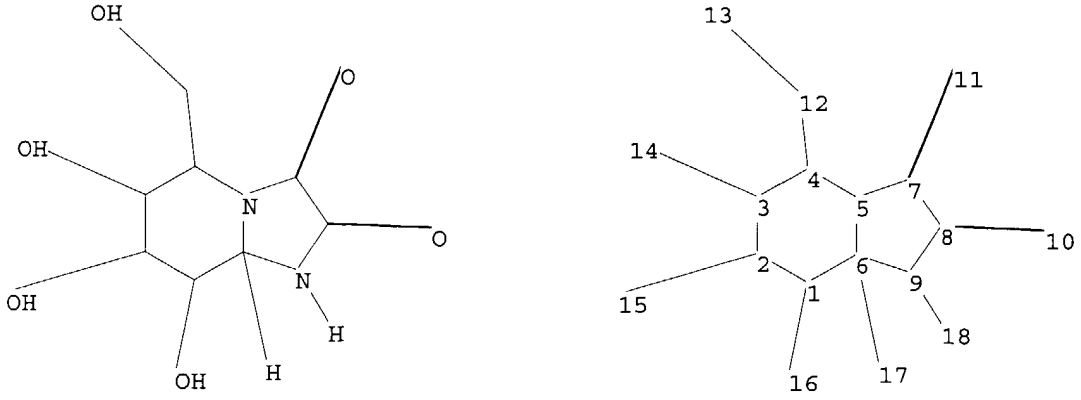


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ring nodes :
1  2  3  4  5  6  7  8  9
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ring bonds :
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exact/norm bonds :
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exact bonds :
4-12  6-17  7-8  9-18
isolated ring systems :
containing 1 :
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Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS
11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS

L1 STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 20:05:23 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 2 TO ITERATE

100.0% PROCESSED 2 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 2 TO 124
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 ful
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FULL SCREEN SEARCH COMPLETED - 32 TO ITERATE

100.0% PROCESSED 32 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

L3 3 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 155.84 156.05

FILE 'CAPLUS' ENTERED AT 20:05:35 ON 02 AUG 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 2 Aug 2004 VOL 141 ISS 6
FILE LAST UPDATED: 1 Aug 2004 (20040801/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 35 L3

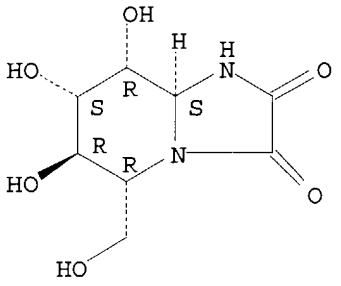
=> d l4 ibib hitstr abs 1-35

L4 ANSWER 1 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:269916 CAPLUS
DOCUMENT NUMBER: 140:304024
TITLE: Process for preparing kifunensine intermediate and kifunensine therefrom
INVENTOR(S): Benjes, Paul Andrew; Jarvis, Ashley Nicholas; Evans, Gary Brian; Painter, Gavin Frank; Dickison, John Adrian; Mitchell, Anthony; Clinch, Keith
PATENT ASSIGNEE(S): Industrial Research Limited, N. Z.
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

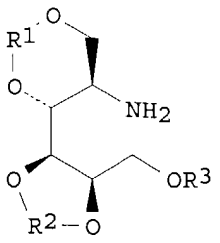
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004063973	A1	20040401	US 2003-615044		20030708
PRIORITY APPLN. INFO.:			NZ 2002-520108	A	20020710

OTHER SOURCE(S): MARPAT 140:304024
IT **109944-15-2P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of kifunensine and intermediates thereof from N-acetyl-D-mannosamine)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



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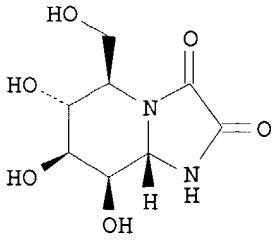
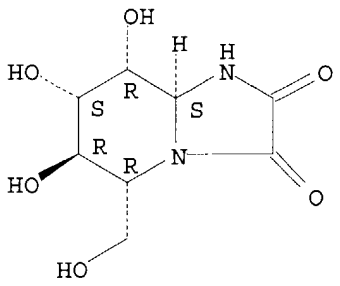


IV

AB The present invention discloses a method for the preparation of a compound of formula I [R1, R2 = protecting groups which, together with the oxygen atoms to which they are attached, form a 5-, 6-, 7- or 8-membered ring; R3 = H, protecting group], or a salt thereof, from an N-protected-D-mannosamine. The method includes protecting the hydroxyl group at the C-6 position of an N-protected-D-mannosamine, to give a 6-O-protected-N-protected-D-mannosamine (II); reducing the C-1 anomeric carbon atom of II to give a 6-O-protected-N-protected-D-mannitol (III); protecting the four hydroxyl groups of the III; and removing the nitrogen atom protecting group and optionally removing the C-6 oxygen atom protecting group to afford I. I is a useful intermediate for the preparation of kifunensine (IV), a potent and selective mannosidase inhibitor.

L4 ANSWER 2 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:880169 CAPLUS
DOCUMENT NUMBER: 140:24809
TITLE: Comparison of Kifunensine and 1-Deoxymannojirimycin Binding to Class I and II α-Mannosidases Demonstrates Different Saccharide Distortions in Inverting and Retaining Catalytic Mechanisms
AUTHOR(S): Shah, Niket; Kuntz, Douglas A.; Rose, David R.
CORPORATE SOURCE: Department of Medical Biophysics, University of Toronto, Toronto, ON, M5G 2M9, Can.
SOURCE: Biochemistry (2003), 42(47), 13812-13816
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2D**, Kifunensine, complexes with α-mannosidase II
RL: PRP (Properties)
(both kifunensine and 1-deoxymannojirimycin exhibit different conformations upon binding class I and II α-mannosidases)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Mannosidases are key enzymes in the eukaryotic N-glycosylation pathway. These enzymes fall into two broad classes (I and II) and are characteristically different in catalytic mechanism, sequence, and structure. Kifunensine is an alkaloid that is a strong inhibitor against class I α-mannosidases but is only a weak inhibitor against class II α-mannosidases. In this paper, the 1.80 Å resolution crystal structure of kifunensine bound to Drosophila melanogaster Golgi α-mannosidase II (dGMII) is presented. Kifunensine adopts a 1,4B boat conformation in the class II dGMII, which contrasts the 1C4 chair conformation seen in class I human endoplasmic reticulum α1,2 mannosidase (hERMI, PDB 1FO2). The observed conformations are higher in conformational energy than the global min. 4C1 conformation, although the conformation in hERMI is closer to the min., as supported by an energy calcn. Differing conformations of 1-deoxymannojirimycin were also observed; i.e., a 4C1 and 1C4 conformation in dGMII and hERMI, resp. Thus, these two α-mannosidase classes distort these inhibitors in distinct manners. This is likely indicative of the binding characteristics of the two different catalytic mechanisms of these enzymes.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:648627 CAPLUS
Correction of: 2003:551314

DOCUMENT NUMBER: 139:161504
Correction of: 139:113661

TITLE: Expression of α-N-acetylglucosaminyl phosphodiesterase proenzyme in furin-deficient mammalian cells and its use in production of lysosomal hydrolases with modified oligosaccharide moiety for treatment of lysosomal storage disease

INVENTOR(S): Canfield, William M.; Kornfeld, Stuart

PATENT ASSIGNEE(S): Genzyme Glycobiology Research Institute, Inc., USA

SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057138	A2	20030717	WO 2002-US38976	20021220
WO 2003057138	A3	20031211		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003143669 A1 20030731 US 2001-23894 20011221

PRIORITY APPLN. INFO.: US 2001-23894 A 20011221

IT **109944-15-2**

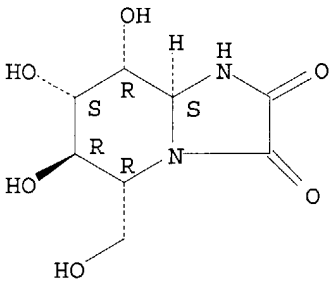
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(mannosidase inhibitor containing, for cell culture; expression of pro-α-N-acetylglucosaminyl phosphodiesterase in furin-deficient mammalian cells and use in production of highly phosphorylated lysosomal hydrolases)

RN 109944-15-2 CAPLUS

CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The present invention provides methods of producing a pro-N-acetylglucosamine-1-phosphodiester α-N-acetyl glucosaminidase (phosphodiester α-GlcNAcase; α-N-acetylglucosaminyl phosphodiesterase), in mammalian cells deficient in the furin proteolytic enzyme and methods of making lysosomal hydrolases having an N-acetylglucosamine-1-phosphate. The phosphodiester α-GlcNAcase comprises a pro-peptide sequence between the signal sequence and the sequence of the mature active form. This pro-peptide sequence is proteolytically cleaved to yield the mature active form of phosphodiester α-GlcNAcase. The activity of uncleaved phosphodiester α-GlcNAcase was significantly lower than the activity of the phosphodiester α-GlcNAcase when the pro-peptide sequence was cleaved. The pro-peptide sequence contains a recognition site for the site-specific protease furin which mediates cleavage of phosphodiester α-GlcNAcase to its mature form. Based on this finding, the invention provides processes of making lysosomal hydrolase in cells which are deficient in furin and thus have the uncleaved form of phosphodiester α-GlcNAcase. By making the lysosomal hydrolases in these cells, the lysosomal hydrolase is modified with an N-acetylglucosamine-1-phosphate moiety and is not removed, or removed at a low efficiency. After expression and recovery of the lysosomal hydrolase from these furin deficient cells, the lysosomal hydrolase can be treated with an active form of phosphodiester α-GlcNAcase thereby removing the N-acetylglucosamine moiety to yield a highly phosphorylated lysosomal enzyme, which can be used in enzyme replacement therapies to treat

patients suffering from lysosomal storage diseases. Thus, the method facilitates a simple and reliable method of producing lysosomal hydrolases with the appropriate phospho-modifications thereby reducing the steps necessary to produce a lysosomal hydrolase for therapeutic or exptl. use. Another object of the present invention is methods for producing a phosphodiester α-GlcNAcase having its pro-peptide intact by culturing cells or selecting cells that are furin deficient, where the selection is preferably conducted using Pseudomonas exotoxin A.

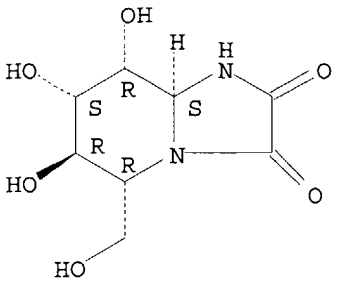
L4 ANSWER 4 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:551314 CAPLUS
DOCUMENT NUMBER: 139:113661
TITLE: Expression of α-N-acetylglucosaminyl phosphodiesterase proenzyme in furin-deficient mammalian cells and its use in production of lysosomal hydrolases with modified oligosaccharide moiety for treatment of lysosomal storage disease
INVENTOR(S): Canfield, William M.; Kornfeld, Stuart
PATENT ASSIGNEE(S): Genzyme Glycobiology Research Institute, Inc., USA
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057138 A2		20030717	WO 2002-US38976	20021220

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR

PRIORITY APPLN. INFO.: US 2001-23894 20011221
IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(mannosidase inhibitor containing, for cell culture; expression of pro-α-N-acetylglucosaminyl phosphodiesterase in furin-deficient mammalian cells and use in production of highly phosphorylated lysosomal hydrolases)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The present invention provides methods of producing a pro-N-acetylglucosamine-1-phosphodiester α-N-acetyl glucosaminidase (phosphodiester α-GlcNAcase; α-N-acetylglucosaminyl phosphodiesterase), in mammalian cells deficient in the furin proteolytic enzyme and methods of making lysosomal hydrolases having an N-acetylglucosamine-1-phosphate. The phosphodiester α-GlcNAcase comprises a pro-peptide sequence between the signal sequence and the sequence of the mature active form. This pro-peptide sequence is proteolytically cleaved to yield the mature active form of phosphodiester α-GlcNAcase. The activity of uncleaved phosphodiester α-GlcNAcase was significantly lower than the activity of the phosphodiester α-GlcNAcase when the pro-peptide sequence was cleaved. The pro-peptide sequence contains a recognition site for the site-specific protease furin which mediates cleavage of phosphodiester α-GlcNAcase to its mature form. Based on this finding, the invention provides processes of making lysosomal hydrolase in cells which are deficient in furin and thus have the uncleaved form of phosphodiester α-GlcNAcase. By making the lysosomal hydrolases in these cells, the lysosomal hydrolase is modified with an N-acetylglucosamine-1-phosphate moiety and is not removed, or removed at a low efficiency. After expression and recovery of the lysosomal hydrolase from these furin deficient cells, the lysosomal hydrolase can be treated with an active form of phosphodiester α-GlcNAcase thereby removing the N-acetylglucosamine moiety to yield a highly phosphorylated lysosomal enzyme, which can be used in enzyme replacement therapies to treat patients suffering from lysosomal storage diseases. Thus, the method facilitates a simple and reliable method of producing lysosomal hydrolases with the appropriate phospho-modifications thereby reducing the steps necessary to produce a lysosomal hydrolase for therapeutic or exptl. use. Another object of the present invention is methods for producing a phosphodiester α-GlcNAcase having its pro-peptide intact by culturing cells or selecting cells that are furin deficient, where the selection is preferably conducted using Pseudomonas exotoxin A.

L4 ANSWER 5 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:550993 CAPLUS
DOCUMENT NUMBER:	139:112730
TITLE:	Method for production of highly phosphorylated human acid β-glucocerebrosidase (GBA), and use of GBA in treating bone or lung tissue of patient with Gaucher's disease
INVENTOR(S):	Canfield, William
PATENT ASSIGNEE(S):	Novazyme Pharmaceuticals, Inc., USA
SOURCE:	U.S. Pat. Appl. Publ., 54 pp. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

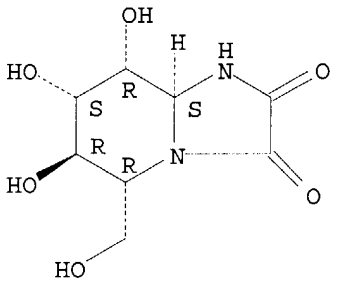
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003133924	A1	20030717	US 2001-24197	20011221

PRIORITY APPLN. INFO.: US 2001-24197 20011221

IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(method for production of highly phosphorylated human acid β-glucocerebrosidase, wherein method involves culturing recombinant cells expressing GBA with at least one α1,2-mannosidase inhibitor, such as)

RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The invention provides a method for producing a highly phosphorylated acid β-glucocerebrosidase (GBA), which involves: (a) culturing cells transfected with polynucleotides encoding a recombinant GBA in the presence of at least one α1,2-mannosidase inhibitor; (b) recovering high mannose recombinant GBA from said cells; (c) contacting said GBA with an isolated N-acetylglucosaminyl phosphotransferase (GlcNAc phosphotransferase) to produce a modified GBA; and (d) contacting said modified GBA with N-acetylglucosamine-1-phosphodiester α-N-acetylglucosaminidase (phosphodiester α-GlcNAcase). The invention also provides for the use of said highly phosphorylated GBA in treating bone or lung tissue of a patient suffering from Gaucher's disease. The invention further provides the cDNA and amino acid sequences of human GBA, phosphodiester α-GlcNAcase, and GlcNAc phosphotransferase. The invention relates that said GlcNAc phosphotransferase comprises an α and β subunit, which reduces substrate specificity, and allows the GlcNAc phosphotransferase to catalyze the transfer of N-acetylglucosamine-1-phosphate from UDP-GlcNAc to the GBA enzyme. The invention discussed that in this method GBA will be phosphorylated which will allow binding to mannose 6 receptors on the surface of lung and bone cells. In so binding to the receptor on these tissues, the problems of the current GBA replacement therapy can be addressed.

L4 ANSWER 6 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511964 CAPLUS
DOCUMENT NUMBER: 139:84071
TITLE: Method of producing glycoproteins having reduced complex carbohydrates in mammalian cells

INVENTOR(S): Canfield, William M.
PATENT ASSIGNEE(S): Novazyme Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003124653	A1	20030703	US 2001-23890	20011221
WO 2003057828	A2	20030717	WO 2002-US38977	20021220
WO 2003057828	A3	20031120		

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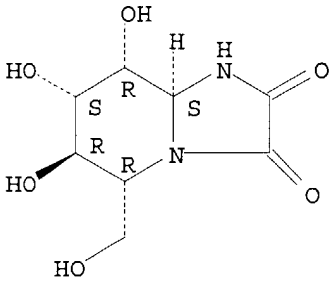
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-23890 A 20011221

IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(producing glycoproteins in complex carbohydrate deficient cells)

RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The present invention provides a method of producing glycoproteins having reduced complex carbohydrates in a mammalian cell, glycoproteins produced by the method and cells that produce the glycoproteins.

L4 ANSWER 7 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:511963 CAPLUS
DOCUMENT NUMBER: 139:84070
TITLE: Methods of producing high mannose glycoproteins in complex carbohydrate deficient cells
INVENTOR(S): Canfield, William M.
PATENT ASSIGNEE(S): Novazyme Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003124652	A1	20030703	US 2001-23889	20011221
WO 2003057710	A2	20030717	WO 2002-US37618	20021219

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

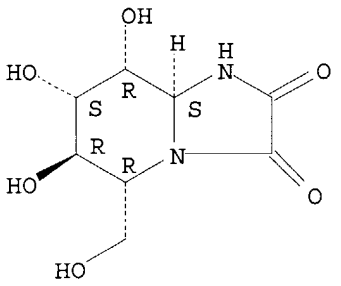
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-23889 A 20011221

IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(producing high mannose glycoproteins in complex carbohydrate deficient cells)

RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

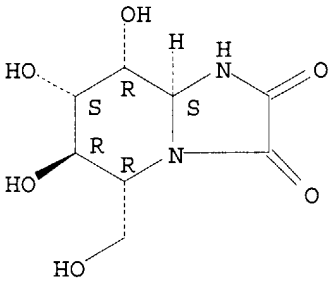


AB The present invention provides a method for producing high mannose glycoproteins in complex carbohydrate deficient cells and the glycoproteins obtained therein.

L4 ANSWER 8 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:708312 CAPLUS
DOCUMENT NUMBER: 138:85523
TITLE: Understanding protein structure-function relationships in family 47 α-1,2-mannosidases through computational docking of ligands
AUTHOR(S): Mulakala, Chandrika; Reilly, Peter J.
CORPORATE SOURCE: Department of Chemical Engineering, Iowa State University, Ames, IA, 50011-2230, USA
SOURCE: Proteins: Structure, Function, and Genetics (2002), 49(1), 125-134

CODEN: PSFGEY; ISSN: 0887-3585
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(structure-function relationships in α-1,2-mannosidases through computational docking of ligands)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Family 47 α-1,2-mannosidases are crucial enzymes involved in N-glycan maturation in the endoplasmic reticulum and Golgi apparatus of eukaryotic cells. High-resolution crystal structures of the human and yeast endoplasmic reticulum α-1,2-mannosidases have been recently determined, the former complexed with the inhibitors 1-deoxymannojirimycin and kifunensine, both of which bind in its active site in the unusual 1C4 conformation. However, unambiguous identification of the catalytic proton donor and nucleophile involved in glycoside bond hydrolysis was not possible from this structural information. In this work, α-D-galactose, α-D-glucose, and α-D-mannose were computationally docked in the active site in the energetically stable 4C1 conformation as well as in the 1C4 conformation to compare their interaction energetics. From these docked structures, a model for substrate and conformer selectivity based on the dimensions of the active site was proposed. α-D-Galactopyranosyl-(1→2)-α-D-mannopyranose, α-D-glucopyranosyl-(1→2)-α-D-mannopyranose, and α-D-mannopyranosyl-(1→2)-α-D-mannopyranose were also docked into the active site with their nonreducing-end residues in the 1C4 and E4 (representing the transition state) conformations. Based on the docked structure of α-D-mannopyranosyl-E4-(1→2)-α-D-mannopyranose, the catalytic acid and base are Glu132 and Glu435, resp.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

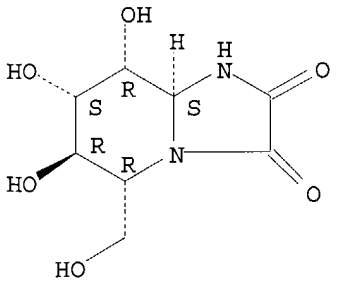
L4 ANSWER 9 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:157596 CAPLUS
DOCUMENT NUMBER: 136:199031
TITLE: High mannose proteins and methods of making high mannose proteins
INVENTOR(S): Kinoshita, Carol A.; Prashsant, Mishra; Borowski, Marianne; Francis-Daniel, Peter
PATENT ASSIGNEE(S): Transkaryotic Therapies, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002015927	A1	20020228	WO 2001-US25882	20010817
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001085061	A5	20020304	AU 2001-85061	20010817
EP 1309340	A1	20030514	EP 2001-964176	20010817
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004506438	T2	20040304	JP 2002-520848	20010817
PRIORITY APPLN. INFO.:			US 2000-641471	A1 20000818
			WO 2001-US25882	W 20010817

IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(high-mannose glucocerebrosidase and methods of making high-mannose glucocerebrosidase using mannosidase inhibitors)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



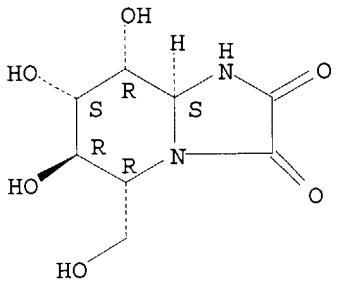
AB The invention features a method of producing a high mannose glucocerebrosidase (hmGCB) which includes: providing a cell which is capable of expressing glucocerebrosidase (GCB), and allowing production of GCB having a precursor oligosaccharide under conditions which prevent the removal of ≥1 mannose residue distal to the pentasaccharide core of the precursor oligosaccharide of GCB, to thereby produce an hmGCB preparation Preferably, the condition which prevents the removal of ≥1 mannose residue distal to the pentasaccharide core is inhibition of a class 1 processing mannosidase and/or a class 2 processing mannosidase. The invention also features an hmGCB preparation and methods of using an hmGCB preparation

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:154067 CAPLUS
DOCUMENT NUMBER: 136:275328
TITLE: Structure of Penicillium citrinum α1,2-mannosidase reveals the basis for differences in specificity of the endoplasmic reticulum and golgi class I enzymes
AUTHOR(S): Lobsanov, Yuri D.; Vallee, Francois; Imberty, Anne; Yoshida, Takashi; Yip, Patrick; Herscovics, Annette; Howell, P. Lynne
CORPORATE SOURCE: Program in Structural Biology and Biochemistry, Research Institute, The Hospital for Sick Children, Toronto, ON, M5G 1X8, Can.
SOURCE: Journal of Biological Chemistry (2002), 277(7), 5620-5630
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2D**, Kifunensine, complexes with α 1,2-mannosidase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(structure of Penicillium citrinum α1,2-mannosidase reveals basis for differences in specificity of endoplasmic reticulum and golgi class I enzymes)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Class I α1,2-mannosidases (glycosylhydrolase family 47) are key enzymes in the maturation of N-glycans. This protein family includes two distinct enzymically active subgroups. Subgroup 1 includes the yeast and human endoplasmic reticulum (ER) α1,2-mannosidases that primarily trim Man9GlcNAc2 to Man8GlcNAc2 isomer B whereas subgroup 2 includes mammalian Golgi α1,2-mannosidases IA, IB, and IC that trim Man9GlcNAc2 to Man5GlcNAc2 via Man8GlcNAc2 isomers A and C. The structure of the catalytic domain of the subgroup 2 α1,2-mannosidases from Penicillium citrinum has been determined by mol. replacement at 2.2-Å resolution The fungal α1,2-mannosidases an (αα)7-helix barrel, very similar to the subgroup 1 yeast and human ER enzymes. The location of the conserved acidic residues of the catalytic site and the binding of the inhibitors, kifunensine and 1-deoxymannojirimycin, to the essential calcium ion are conserved in the fungal enzyme. However, there

are major structural differences in the oligosaccharide binding site between the two α1,2-mannosidases subgroups. In the subgroup 1 enzymes, an arginine residue plays a critical role in stabilizing the oligosaccharide substrate. In the fungal α1,2-mannosidase this arginine is replaced by glycine. This replacement and other sequence variations result in a more spacious carbohydrate binding site. Modeling studies of interactions between the yeast, human and fungal enzymes with different Man8GlcNAc2 isomers indicate that there is a greater degree of freedom to bind the oligosaccharide in the active site of the fungal enzyme than in the yeast and human ER α1,2-mannosidases.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

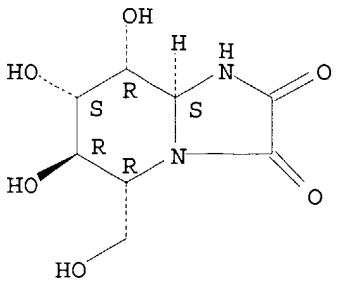
L4 ANSWER 11 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:545469 CAPLUS
DOCUMENT NUMBER: 135:102588
TITLE: Methods using glucosidase inhibitors or other compounds to treat α1-antitrypsin deficiency
INVENTOR(S): Perlmutter, David; Marcus, Nancy Y.
PATENT ASSIGNEE(S): Washington University, USA
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052830	A2	20010726	WO 2001-US2215	20010122
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 2002006909	A1	20020117	US 2001-768029	20010122
US 6656912	B2	20031202		
EP 1250129	A2	20021023	EP 2001-902140	20010122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.:
US 2000-177392P P 20000120
US 2000-177472P P 20000121
WO 2001-US2215 W 20010122

IT **109944-15-2**, Kifunensine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucosidase inhibitors or other compds. to treat α1-antitrypsin deficiency)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Inhibitors of glucosidase, especially those related to castanospermine, are effective in preventing or ameliorating conditions such as liver damage and emphysema that are present in individuals who produce a mutant form of antitrypsin α1-ATZ. Also effective in the method of the invention are imino sugars and their reduced forms in general as well as phenylbutyric acid. These compds. enhance the secretion of the mutant form, which retains substantial biol. activity, and do not impair its degradation in the endoplasmic reticulum.

L4 ANSWER 12 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:208390 CAPLUS
DOCUMENT NUMBER: 134:248843
TITLE: Use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases
INVENTOR(S): Canfield, William M.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019955	A2	20010322	WO 2000-US21970	20000914
WO 2001019955	A3	20011004		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6534300	B1	20030318	US 2000-635872	20000810
US 6537785	B1	20030325	US 2000-636077	20000810
US 6642038	B1	20031104	US 2000-636060	20000810
AU 2000073303	A5	20010417	AU 2000-73303	20000914
BR 2000014514	A	20020723	BR 2000-14514	20000914
EP 1224266	A2	20020724	EP 2000-961335	20000914
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003509043	T2	20030311	JP 2001-523727	20000914

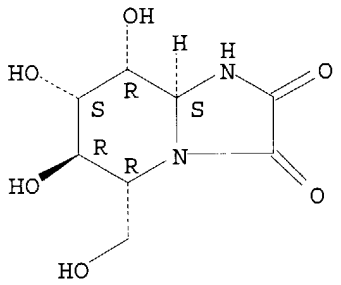
US 2002025550	A1	20020228	US 2001-895072		20010702
US 2002150981	A1	20021017	US 2001-986552		20011109
US 6670165	B2	20031230			
US 2003148460	A1	20030807	US 2002-306686		20021129
PRIORITY APPLN. INFO.:			US 1999-153831P	P	19990914
			US 2000-635872	A1	20000810
			US 2000-636596	A3	20000810
			WO 2000-US21970	W	20000914

IT **109944-15-2**, Kifunensine
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(use of GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase in production of highly phosphorylated lysosomal hydrolases useful in treatment of lysosomal storage diseases)

RN 109944-15-2 CAPLUS

CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



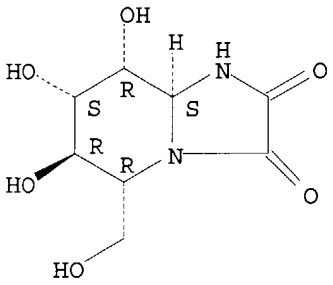
AB The lysosomal targeting pathway enzymes GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase and uses in production of highly phosphorylated lysosomal hydrolases that can be used to treat lysosomal storage diseases, are disclosed. Generally, the nucleic acid mols. coding for the enzymes are incorporated into expression vectors that are used to transfect host cells that express the enzymes. The expressed enzymes are recovered using monoclonal antibodies capable of selectively binding to bovine GlcNAc-phosphotransferase and to bovine phosphodiester α-GlcNAcase. Lysosomal hydrolases having high mannose structures are treated with GlcNAc-phosphotransferase and phosphodiester α-GlcNAcase resulting in the production of asparagine-linked oligosaccharides that are highly modified with mannose 6-phosphate ("M6P"). The treated hydrolase binds to M6P receptors on the cell membrane and is transported into the cell and delivered to the lysosome where it can perform its normal or a desired function. The highly phosphorylated lysosomal hydrolases are readily taken into the cell and into the lysosome during enzyme replacement therapy procedures.

L4 ANSWER 13 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:34613 CAPLUS
DOCUMENT NUMBER: 134:189984
TITLE: Structural basis for catalysis and inhibition of N-glycan processing class I α1,2-mannosidases
AUTHOR(S): Vallee, Francois; Karaveg, Khanita; Herscovics, Annette; Moremen, Kelley W.; Howell, P. Lynne
CORPORATE SOURCE: Program in Structural Biology and Biochemistry, Research Institute, Hospital for Sick Children, Toronto, ON, M5G 1X8, Can.

SOURCE: Journal of Biological Chemistry (2000), 275(52), 41287-41298
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **109944-15-2D**, Kifunensine, complexes with α1,2-mannosidase
RL: PRP (Properties)
(crystal structure of endoplasmic reticulum class I α1,2-mannosidase in absence and presence of kifunensine and deoxymannojirimycin)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

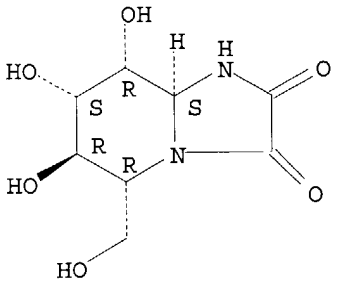


AB Endoplasmic reticulum (ER) class I α1,2-mannosidase (also known as ER α-mannosidase I) is a critical enzyme in the maturation of N-linked oligosaccharides and ER-associated degradation Trimming of a single mannose residue acts as a signal to target misfolded glycoproteins for degradation by the proteasome. Crystal structures of the catalytic domain of human ER class I α1,2-mannosidase have been determined both in the presence and absence of the potent inhibitors kifunensine and 1-deoxymannojirimycin. Both inhibitors bind to the protein at the bottom of the active-site cavity, with the essential calcium ion coordinating the 0-2' and 0-3' hydroxyls and stabilizing the six-membered rings of both inhibitors in a 1C4 conformation. This is the first direct evidence of the role of the calcium ion. The lack of major conformational changes upon inhibitor binding and structural comparisons with the yeast α1,2-mannosidase enzyme-product complex suggest that this class of inverting enzymes has a novel catalytic mechanism. The structures also provide insight into the specificity of this class of enzymes and provide a blueprint for the future design of novel inhibitors that prevent degradation of misfolded proteins in genetic diseases.
REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:34546 CAPLUS
DOCUMENT NUMBER: 134:205366
TITLE: Endoplasmic reticulum (ER)-associated degradation of misfolded N-linked glycoproteins is suppressed upon inhibition of ER mannosidase I
AUTHOR(S): Tokunaga, Fuminori; Brostrom, Charles; Koide, Takehiko; Arvan, Peter
CORPORATE SOURCE: Department of Life Science, Himeji Institute of

Technology, Harima Science Garden City, 678-1277, Japan
SOURCE: Journal of Biological Chemistry (2000), 275(52), 40757-40764
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endoplasmic reticulum (ER)-associated degradation of misfolded N-linked glycoproteins is suppressed upon inhibition of ER mannosidase I)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB To examine the role of early carbohydrate recognition/trimming reactions in targeting endoplasmic reticulum (ER)-retained, misfolded glycoproteins for ER-associated degradation (ERAD), we have stably expressed the cog thyroglobulin (Tg) mutant cDNA in Chinese hamster ovary cells. We found that inhibitors of ER mannosidase I (but not other glycosidases) acutely suppressed Cog Tg degradation and also perturbed the ERAD process for Tg reduced with dithiothreitol as well as for γ-carboxylation-deficient protein C expressed in warfarin-treated baby hamster kidney cells. Kifunensine inhibition of ER mannosidase I also suppressed ERAD in castanospermine-treated cells; thus, suppression of ERAD does not require lectin-like binding of ER chaperones calnexin and calreticulin to monoglucosylated oligosaccharides. Notably, the undegraded protein fraction remained completely microsome-associated In pulse-chase studies, kifunensine-sensitive degradation was still inhibitable even 1 h after Tg synthesis. Intriguingly, chronic treatment with kifunensine caused a 3-fold accumulation of Cog Tg in Chinese hamster ovary cells and did not lead to significant induction of the ER unfolded protein response. We hypothesize that, in a manner not requiring lectin-like activity of calnexin/calreticulin, the recognition or processing of a specific branched N-linked mannose structure enhances the efficiency of glycoprotein retrotranslocation from the ER lumen.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:31662 CAPLUS
DOCUMENT NUMBER: 134:96289
TITLE: Cloning and cDNA sequence of a novel human

α-1,2-mannosidase which triggers degradation of misfolded glycoproteins and its therapeutic uses
INVENTOR(S): Herscovics, Annette A.; Tremblay, Linda O.
PATENT ASSIGNEE(S): McGill University, Can.
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

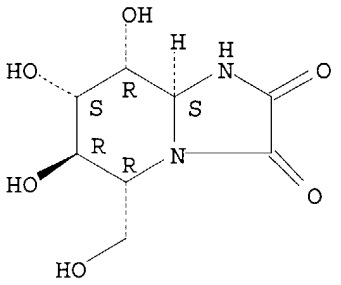
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002586	A1	20010111	WO 2000-CA775	20000628

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-140992P P 19990629

IT **109944-15-2**, Kifunensine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(α-1,2-mannosidase inhibited by; cloning and cDNA sequence of novel human α-1,2-mannosidase which triggers degradation of misfolded glycoproteins and its therapeutic uses)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



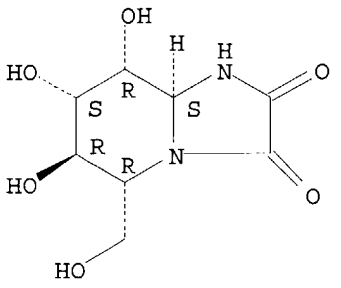
AB The present invention provides the isolation, expression, and properties of a novel human cDNA encoding a type II membrane protein of 79.5 kDA with sequence similarity to class I α-1,2-mannosidases. The catalytic domain of the enzyme was expressed as a secreted protein in Pichia pastoris. The recombinant enzyme removes a single mannose residue from Man9GlcNAc in the endoplasmic reticulum to produce Man8GlcNAc2 isomer B, the form lacking the middle-arm terminal α-1,2-mannose. The enzyme requires calcium for activity and is inhibited by both 1-deoxymannojirimycin and kifunensine. The enzyme may trigger degradation of misfolded glycoproteins. The present invention also relates to an agonist or antagonist of the α-1,2-mannosidase for activating or inhibiting the enzyme. The present invention also relates to a method for the

treatment of genetic diseases resulting in misfolding of glycoproteins in a patient, which comprises administering an antagonist of α-1,2-mannosidase enzyme for transiently inhibiting the enzyme, thereby stabilizing misfolded glycoproteins and preventing their degradation

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:81208 CAPLUS
DOCUMENT NUMBER: 132:217071
TITLE: Glucosidase and mannosidase inhibitors mediate increased secretion of mutant α1-antitrypsin Z
AUTHOR(S): Marcus, Nancy Y.; Perlmutter, David H.
CORPORATE SOURCE: Departments of Pediatrics, Cell Biology and Physiology, Division of Gastroenterology and Nutrition, Washington University School of Medicine, Children's Hospital, St. Louis, MO, 63110, USA
SOURCE: Journal of Biological Chemistry (2000), 275(3), 1987-1992
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucosidase and mannosidase inhibitors mediate increased secretion of mutant α1-antitrypsin Z)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB It is now well known that the addition and trimming of oligosaccharide side chains during post-translational modification play an important role in determining the fate of secretory, membrane, and lysosomal glycoproteins. Recent studies have suggested that trimming of oligosaccharide side chains also plays a role in the degradation of misfolded glycoproteins as a part of the quality control mechanism of the endoplasmic reticulum (ER). In this study, we examined the effect of several inhibitors of carbohydrate processing on the fate of the misfolded secretory protein α1-antitrypsin Z. Retention of this misfolded glycoprotein in the ER of liver cells in the classical form of α1-antitrypsin (α1-AT) deficiency is associated with severe liver injury and hepatocellular carcinoma and lack of its secretion is associated with

destructive lung disease/emphysema. The results show marked alterations in the fate of α1-antitrypsin Z (α1-ATZ). Indeed, one glucosidase inhibitor, castanospermine (CST), and two mannosidase inhibitors, kifunensine (KIF) and deoxymannojirimycin (DMJ), mediate marked increases in secretion of α1-ATZ by distinct mechanisms. The effects of these inhibitors on secretion have interesting implications for our understanding of the quality control apparatus of the ER. These inhibitors may also constitute models for development of addnl. drugs for chemoprophylaxis of liver injury and emphysema in patients with α1-AT deficiency.

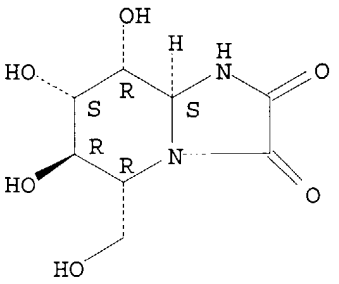
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:518252 CAPLUS
DOCUMENT NUMBER: 131:153726
TITLE: Inhibition of bacterial binding by high-mannose oligosaccharides, and method for the treatment of Gram-negative bacterial infections
INVENTOR(S): Smith, Sam; Elbein, Alan D.; Pan, Y. T.
PATENT ASSIGNEE(S): The Board of Trustees of the University of Arkansas, USA
SOURCE: U.S., 20 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5939279	A	19990817	US 1997-932876	19970918
PRIORITY APPLN. INFO.:			US 1997-932876	19970918

IT **109944-15-2**, Kifunensine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-mannose oligosaccharides for inhibition of bacterial binding, and method for treatment of Gram-neg. bacterial infections)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

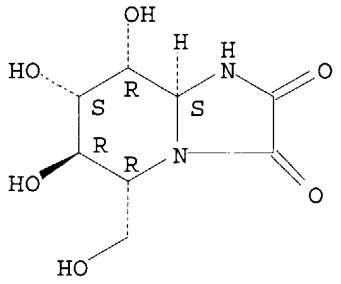


AB A method is provided for the treatment of Gram-neg. bacterial infections using high-mannose containing oligosaccharides. Specifically, the invention describes the use of Man9 (GlcNAc)2-hydrophobic glycopeptides (i.e.

tyrosinamide) to block adhesion of the bacteria pili to the oligosaccharide of the host cells plasma membrane in infections of Enterobacter cloacae and other Enterobacter and gram-neg. species.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:45702 CAPLUS
DOCUMENT NUMBER: 126:142337
TITLE: Evaluation of the early processing routes of N-linked oligosaccharides of glycoproteins through the characterization of Man8GlcNAc2 isomers: evidence that endomannosidase functions in vivo in the absence of a glucosidase blockage
AUTHOR(S): Weng, Shuai; Spiro, Robert G.
CORPORATE SOURCE: Dep. biol. Chem. Med., Harvard Med. Sch. Joslin Diabetes Cent., Boston, MA, 02215, USA
SOURCE: Glycobiology (1996), 6(8), 861-868
CODEN: GLYCE3; ISSN: 0959-6658
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(evaluation of early processing routes of N-linked oligosaccharides of glycoproteins through characterization of Man8GlcNAc2 isomers demonstrates that endomannosidase functions in vivo in absence of a glucosidase blockage)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



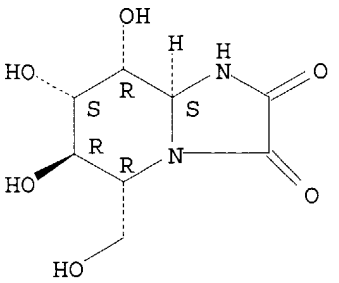
AB Since it has become apparent that the early processing of the N-linked oligosaccharides of glycoproteins can proceed by several routes, we undertook to determine whether the isomeric nature of Man8GlcNAc2, which is the first intermediate with the potential for structural diversity, can provide information relating to the pathways utilized in various intact cultured cells as well as in the total membrane fraction derived from these cells (BW5147.3, HepG2, HL-60, F-9, and MDCK). With the use of kifunensine (KIF) to block processing by Golgi mannosidase I, it could be shown that a substantial amount of Man8GlcNAc2 components in which the terminal mannose is missing in the α1,3-linked and α1,6-linked chain (isomers A and C, resp.) are produced, although in the absence of the inhibitor only the B-isomer, in which the mannose of the middle chain has been excised, was apparent. Our findings in vivo and in vitro suggest

that the distinctive Man8GlcNAc2 product of endomannosidase (isomer A) and of ER mannosidase II (isomer C) are not evident in the absence of KIF since they are rapidly degraded by Golgi mannosidase I, which is located in an intracellular compartment distal to the other two enzymes and itself exclusively generates the Man8GlcNAc2 isomer B. Investigations carried out in HepG2 cells indicated that glycoproteins with N-linked oligosaccharide whose processing has been blocked by KIF at the Man8GlcNAc2 isomer A and C stage can nevertheless be effectively secreted. The observation of endomannosidase action made it possible to demonstrate the action of this enzyme in vivo without employing a glucosidase blockade and to show that a substantial amount of the degluocsylation of N-linked oligosaccharides is carried out by this enzyme.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:409888 CAPLUS
DOCUMENT NUMBER: 121:9888
TITLE: Microbial Oxidation of Aromatics in Enantiocontrolled Synthesis. 2. Rational Design of Aza Sugars (endo-Nitrogenous). Total Synthesis of (&)-Kifunensine, Mannojirimycin, and Other Glycosidase Inhibitors
AUTHOR(S): Hudlicky, Tomas; Rouden, Jacques; Luna, Hector; Allen, Scott
CORPORATE SOURCE: Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA, 24061-0212, USA
SOURCE: Journal of the American Chemical Society (1994), 116(12), 5099-107
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2P**, Kifunensine
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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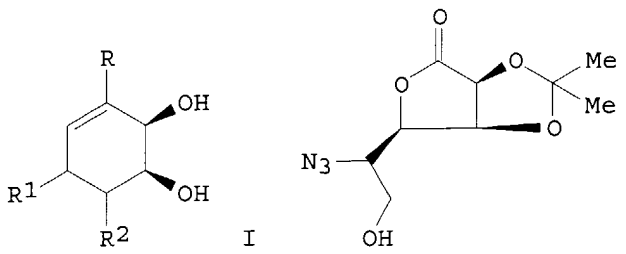
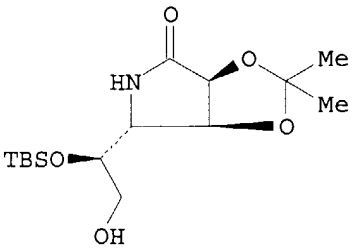
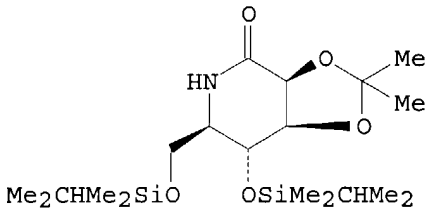


I

II



III

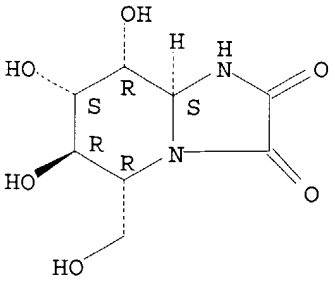


IV

AB A general method of synthesis for lactones and lactams related to carbohydrates has been developed that relies on the biocatalytic generation of 1-chloro-2,3-dihydroxycyclohexa-4,6-diene, obtained in excellent yield by fermentation of chlorobenzene with Pseudomonas putida 39D, followed by further functionalization to nitrogen-substituted cyclitols. These amino or azido cyclitols of type I (R = H, Cl, R1 = OH, R2 = N3, NH2, NHBn; R1 = N3, NH2, NHBn, R2 = OH) are then subjected to controlled ozonolysis, which yields either lactones, e.g. II, or lactams, e.g. III and IV. Such compds. are useful intermediates for the preparation of aza sugars. Mannojirimycin has been synthesized in seven steps from chlorobenzene. Kifunensine has been prepared in 11 steps from chlorobenzene following an intersection with Hashimoto's procedure. Full exptl. and spectral details are provided for all compds. The potential of this general method and implications of the disclosed design features in the field of amino sugar and aza sugar synthesis are indicated.

L4 ANSWER 20 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:573410 CAPLUS
DOCUMENT NUMBER: 119:173410
TITLE: FK506 and kifunensine, new immunomodulators of microbial origin
AUTHOR(S): Izumi, Shizue; Okuhara, Masakuni
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Tanpakushitsu Kakusan Koso (1993), 38(11), 1800-12
CODEN: TAKKAJ; ISSN: 0039-9450
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
IT **109944-15-2**
RL: BIOL (Biological study)
(from Kitasatosporia kifunense, immunosuppression by, mechanism of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

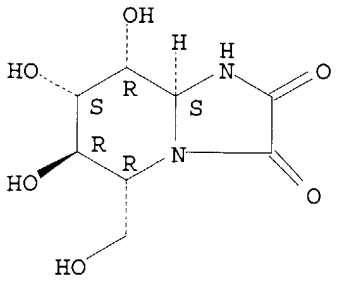
Absolute stereochemistry.



AB A review with 98 refs., on the FK506 and kifunensine. Discovery, in vitro and in vivo activities, and clin. results of FK506 are discussed. FK506 inhibits the interleukin 2 (IL-2) production in T cells triggered by the stimulation of T cell receptor (TCR)/CD3 complex, and not by the stimulation of CD28. The inhibition is by the inhibition of the binding of transacting factors to IL-2 gene specifically. FK506 binds with FK506 binding protein (FBK) possessing peptidylpropyl cis trans isomerase (PPIase) as in the case of cyclosporin A. Kifunensine derived from Kitasatosporia kifunensine No.9482 enhances the expression of major histocompatibility antigen (MHC) class II. Kifunensine exhibits immunosuppression activity shown in adjuvant arthritis, type II collagen arthritis, and skin allograft in rodent models. Unfortunately kifunensine exhibits certain toxicity.

L4 ANSWER 21 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:539647 CAPLUS
DOCUMENT NUMBER: 119:139647
TITLE: Total synthesis of (+)-kifunensine, a potent glycosidase inhibitor
AUTHOR(S): Rouden, Jacques; Hudlicky, Tomas
CORPORATE SOURCE: Dep. Chem., Virginia Polytech. Inst. and State Univ., Blacksburg, VA, 24061, USA
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1993), (10), 1095-7
CODEN: JCPRB4; ISSN: 0300-922X
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2P**, (+)-Kifunensine
RL: PREP (Preparation)
(total synthesis from chlorobenzene)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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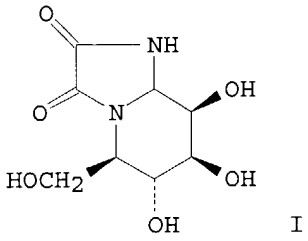
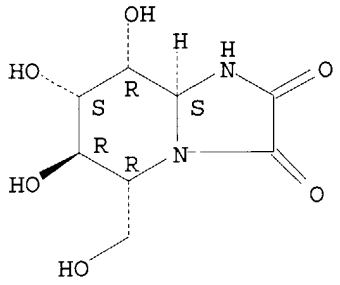


I

AB (+)-Kifunensine (I), a potent inhibitor of mannosidase I, has been synthesized in 13 steps from chlorobenzene via stereocontrolled peripheral functionalization of cis-3-chlorocyclohexa-3,5-dienediol.

L4 ANSWER 22 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:124218 CAPLUS
DOCUMENT NUMBER: 118:124218
TITLE: Enzymatic hydroxylation of arene and symmetry considerations in efficient synthetic design of oxygenated natural products
AUTHOR(S): Hudlicky, Tomas; Fan, Rulin; Luna, Hector; Olivo, Horacio; Price, John
CORPORATE SOURCE: Chem. Dep., Virginia Tech, Blacksburg, VA, 24081, USA
SOURCE: Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1993), 32B(1), 154-8
CODEN: IJSBDB; ISSN: 0376-4699
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2P**, Kifunensine
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, from chlorobenzene)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

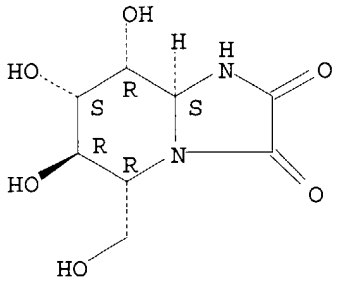


AB A lecture with 9 refs. Microbial oxidation of substituted aromatic compds. with
mutant strains of Pseudomonas putida (39D) yields the corresponding arene cis-diols in efficient quantities and >99% enantiomeric excess. The use

of these synthons in the practical preparation of oxygenated natural products is described with emphasis on the importance of symmetry considerations during synthetic planning in order to achieve enantiodivergent prepns. of target compds. The applications are highlighted by discussion of the syntheses of the following compds. from chlorobenzene: (+)- and (-)-erythrose, (+)- and (-)-ribonolactone, (+)- and (-)-trihydroxyheliotridane, (+)- and (-)-pinitol, kifunensine, lycoricidine and a model study for a short synthesis of (-)-morphine. The conclusion of the lecture places in perspective the use of halogenated aroms. in the chiral pool supply with the potential of efficiently replacing sugars. Brevity and efficiency of the synthetic sequences are emphasized.

L4 ANSWER 23 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:655871 CAPLUS
DOCUMENT NUMBER: 115:255871
TITLE: Structure of kifunensine, a new immunomodulator isolated from an actinomycete
AUTHOR(S): Kayakiri, Hiroshi; Takase, Shigehiro; Shibata, Toshihiro; Hashimoto, Masashi; Tada, Toshiji; Koda, Shigetaka
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1991), 39(6), 1378-81
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: PRP (Properties)
(crystal structure and absolute configuration of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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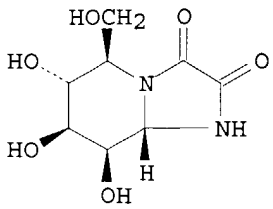
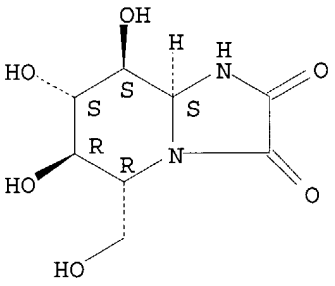


I

AB The mol. structure and absolute configuration of kifunensine was determined as I by
chemical, physicochem., and x-ray crystallog. anal.

L4 ANSWER 24 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:632688 CAPLUS
DOCUMENT NUMBER: 115:232688
TITLE: Synthesis of 8-epi-kifunensine
AUTHOR(S): Kayakiri, Hiroshi; Oku, Teruo; Hashimoto, Masashi
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1991), 39(6), 1397-401
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **129314-18-7P**, 8-epi-Kifunensine
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and crystal and mol. structure of)
RN 129314-18-7 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, [5R-(5α,6β,7α,8β,8aα)]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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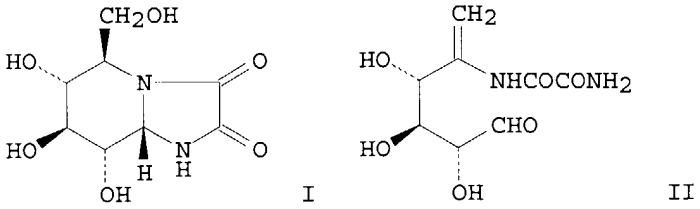


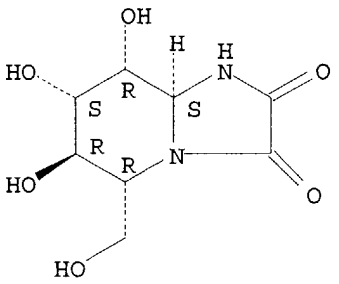
I II

AB A synthesis of 8-epi-kifunensine (I) in optically active form was achieved starting from D-glucose via a modified double cyclization of the oxamide-hemiacetal precursor II with 2,4-dimethoxybenzylamine as a key step. The structure of I was confirmed by x-ray crystal anal.

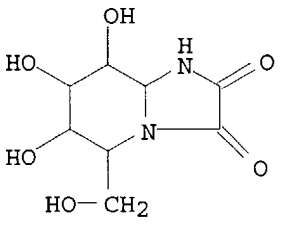
L4 ANSWER 25 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:583732 CAPLUS
DOCUMENT NUMBER: 115:183732

TITLE: Synthesis of kifunensine, an immunomodulating substance isolated from a microbial source
AUTHOR(S): Kayakiri, Hiroshi; Kasahara, Chiyoshi; Nakamura, Katsuya; Oku, Teruo; Hashimoto, Masashi
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1991), 39(6), 1392-6
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2P**, Kifunensine **136598-17-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 136598-17-9 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, [5R-(5α,6β,7α,8α,8aβ)]-
(9CI) (CA INDEX NAME)



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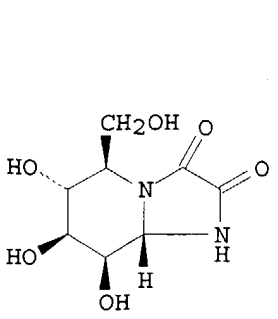
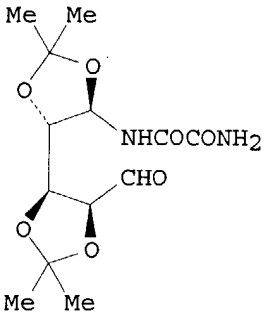


I



II

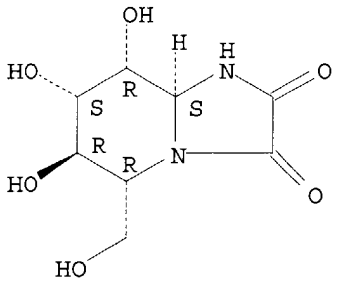
AB Kifunensine (I), a novel immunomodulator isolated from an actinomycete, was enantiospecifically synthesized from D-mannosamine via a double cyclization of the oxamide-aldehyde precursor II with NH3 as a key step. The absolute stereochem. of natural kifunensine was confirmed to be the d-form.

L4 ANSWER 26 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:408803 CAPLUS
DOCUMENT NUMBER: 115:8803
TITLE: 2,3-Dioxoimidazo[1,2-a]pyridine derivatives as immunomodulators
INVENTOR(S): Oku, Teruo; Kashahara, Chiyoshi; Kayakiri, Hiroshi; Nakamura, Katsuya; Hashimoto, Shinji
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03014580	A2	19910123	JP 1989-149228	19890612
PRIORITY APPLN. INFO.:			JP 1989-149228	19890612

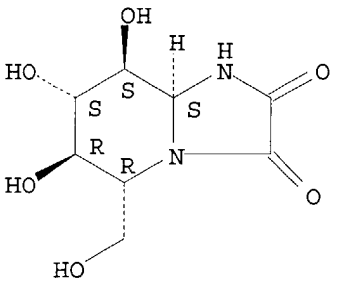
OTHER SOURCE(S): MARPAT 115:8803
IT **109944-15-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-methylation of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

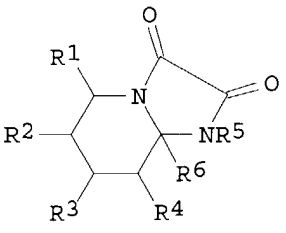


IT **129314-18-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as immunomodulator)
RN 129314-18-7 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, [5R-(5α,6β,7α,8β,8aα)]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



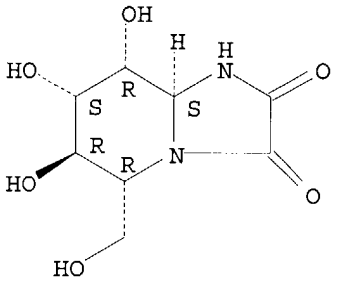
I

AB The title derivs. I [R1 = lower (un)protected hydroxyalkyl; R2, R3 = (un)protected hydroxy; R4 = H, (un)protected hydroxy; R5 = H, halo, OH, lower alkoxy; R6 = H, lower alkyl, lower carboxyalkyl which may be esterified, lower alkoxyaralkyl; R1, R2 = protected hydroxy when R6 = H], useful as antagonists especially for leukocytic immunosuppressants (no data), are prepared 5-Deoxy-2,3:4,6-di-O-isopropylidene-5-oxamylamino-D-mannose, prepared from D-mannosamine hydrochloride and H2NCOCO2H in 5 steps, was treated with NH3/MeOH under stirring at room temperature for 5 h to give 55.2% (5R,6R,7S,8R,8aS)-I (R1R2 = CH2OCMe2O, R3R4 = OCMe2O, R5 = R6 = H).

L4 ANSWER 27 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:405933 CAPLUS
DOCUMENT NUMBER: 115:5933
TITLE: Kifunensine inhibits glycoprotein processing and the function of the modified LDL receptor in endothelial cells
AUTHOR(S): Elbein, Alan D.; Kerbacher, James K.; Schwartz, Colin J.; Sprague, Eugene A.
CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA
SOURCE: Archives of Biochemistry and Biophysics (1991), 288(1), 177-84
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BIOL (Biological study)
(glycoprotein processing and scavenger receptor function inhibition by, in endothelial cells)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

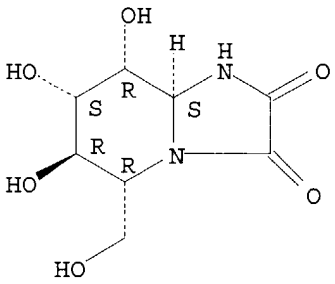


AB Kifunensine is an alkaloid that is produced by the actinomycete Kitasatosporia kifunense and resembles the cyclic oxamide derivative of 1-aminodeoxymannojirimycin in structure. When bovine aorta endothelial cells were grown in the presence of 1 μg kifunensine/mL, there was a 75% inhibition in the ability of these cells to degrade 125I-labeled acetyl-low-d. lipoproteins (LDL), but this inhibitor appeared to have little or no effect on the ability of either endothelial cells or fibroblasts to degrade 125I-labeled LDL, even at kifunensine concns. of 10 μg/mL. Kifunensine also decreased the binding of the labeled acetyl-LDL by the scavenger receptor of the endothelial cells, but the amount of this inhibition relative to controls was significantly less than that of the degradation, suggesting that kifunensine affects 2 different steps of acetyl-LDL metabolism in these cells. Endothelial cells grown in the presence of 10 μg/mL of kifunensine had only half the activity of the lysosomal enzymes, β-hexosaminidase, and proteases, as did control cells, although kifunensine did not affect [3H]leucine incorporation into protein. Thus, kifunensine apparently affects the activity of (some) lysosomal enzymes in an as yet undefined manner.

L4 ANSWER 28 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:611654 CAPLUS
DOCUMENT NUMBER: 113:211654
TITLE: Total synthesis of kifunensine and 8-epi-kifunensine
AUTHOR(S): Kayakiri, H.; Kasahara, C.; Takase, S.; Oku, T.;

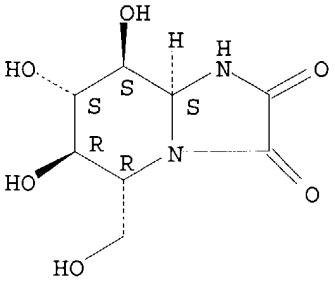
Hashimoto, M.
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Japan
SOURCE: Tennen Yuki Kagobutsu Toronkai Koen Yoshishu (1989), 31st, 159-66
CODEN: TYKYDS
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
IT **109944-15-2P**, Kifunensine **129314-18-7P**, 8-epi-Kifunensine
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 129314-18-7 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, [5R-(5α,6β,7α,8β,8aα)]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

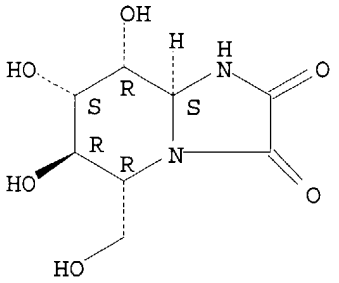


AB A report from a symposium describing the total synthesis of kifunensine and 8-epi-kifunesine.

L4 ANSWER 29 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:607041 CAPLUS
DOCUMENT NUMBER: 113:207041
TITLE: Kifunensine, a potent inhibitor of the glycoprotein processing mannosidase I
AUTHOR(S): Elbein, Alan D.; Tropea, Joseph E.; Mitchell, Mike; Kaushal, Gur P.
CORPORATE SOURCE: Health Sci. Cent., Univ. Texas, San Antonio, TX, 78284, USA

SOURCE: Journal of Biological Chemistry (1990), 265(26), 15599-605
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**, Kifunensine
RL: BIOL (Biological study)
(glycoprotein processing mannosidase I inhibition by)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

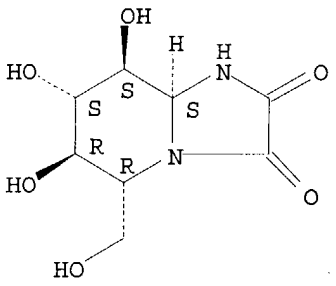


AB Kifunensine, produced by the actinomycete Kitasatosporia kifunense 9482, is an alkaloid that corresponds to a cyclic oxamide derivative of 1-amino manojirimycin. This compound was reported to be a weak inhibitor of jack bean α-mannosidase (IC50 of 1.2 + 10-4 M). This study shows that it was a poor inhibitor of jack bean and mung bean aryl-α-mannosidases, but it was a very potent inhibitor of the plant glycoprotein processing enzyme, mannosidase I (IC50 of 2-5 + 10-8 M), when [3H]mannose-labeled Man9GlcNAc was used as substrate. However, kifunensine was inactive toward the plant mannosidase II. Studies with rat liver microsomes also indicated that kifunensine inhibited the Golgi mannosidase I, but probably does not inhibit the endoplasmic reticulum mannosidase. Kifunensine was tested in cell culture by examining its ability to inhibit processing of the influenza viral glycoproteins in Madin-Darby canine kidney cells. Thus, when kifunensine was placed in the incubation medium at concns. of 1 μg/mL or higher, it caused a complete shift in the structure of the N-linked oligosaccharides from complex chains to Man9(GlcNAc)2 structure, in keeping with its inhibition of mannosidase I. On the other hand, even at 50 μg/mL, deoxymannojirimycin did not prevent the formation of all complex chains. Thus kifunensine appears to be one of the most effective glycoprotein processing inhibitors observed thus far, and knowledge of its structure may lead to the development of potent inhibitors of other processing enzymes.

L4 ANSWER 30 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:532637 CAPLUS
DOCUMENT NUMBER: 113:132637
TITLE: Synthesis of 8-epi-kifunensine
AUTHOR(S): Kayakiri, Hiroshi; Oku, Teruo; Hashimoto, Masashi
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1990), 38(1), 293-5
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:132637
IT **129314-18-7P**, 8-epi-Kifunensine
RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(crystal structure and total synthesis of)
RN 129314-18-7 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, [5R-(5α,6β,7α,8β,8aα)]-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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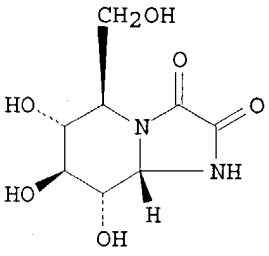
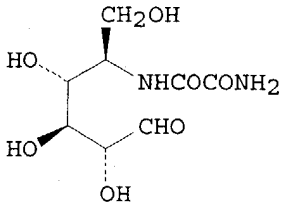


I



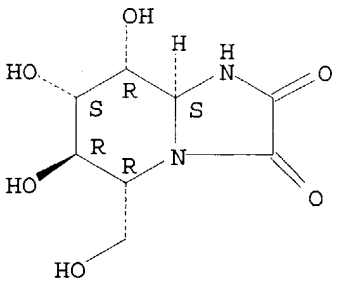
II

AB 8-epi-Kifunensine (I) was synthesized from D-glucose by a route involving a double cyclization of II as a key step. The structure of I was confirmed by crystal data.

L4 ANSWER 31 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:497878 CAPLUS
DOCUMENT NUMBER: 113:97878
TITLE: Synthesis of kifunensine, an immunomodulating substance isolated from microbial source
AUTHOR(S): Kayakiri, Hiroshi; Kasahara, Chiyoshi; Oku, Teruo; Hashimoto, Masashi
CORPORATE SOURCE: Exploratory Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Tetrahedron Letters (1990), 31(2), 225-6
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:97878
IT **109944-15-2P**, Kifunensine
RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of)

RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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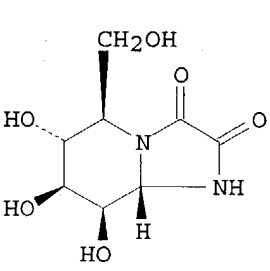
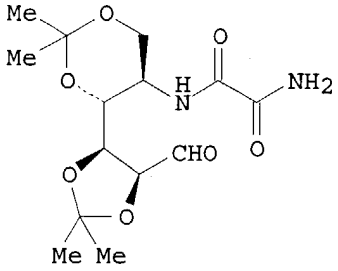


I



II

AB A synthesis of kifunensine (I) was achieved by a route involving, as a key step, a double cyclization of aldehyde II with ammonia.

L4 ANSWER 32 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:223253 CAPLUS
DOCUMENT NUMBER: 112:223253
TITLE: FR 900494 for therapy of autoimmune diseases
INVENTOR(S): Kaizu, Tsutomu; Miyata, Susumu; Okamoto, Masanori; Okuhara, Masakuni
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01238531	A2	19890922	JP 1988-66884	19880319

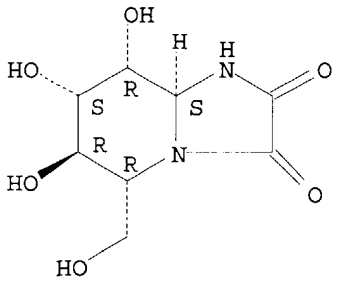
PRIORITY APPLN. INFO.: JP 1988-66884 19880319

IT **109944-15-2**, FR 900494 **109944-15-2D**, FR 900494, salts
RL: BIOL (Biological study)
(autoimmune disease treatment by, as inflammation inhibitor)

RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-

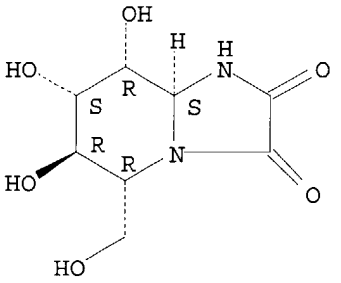
(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

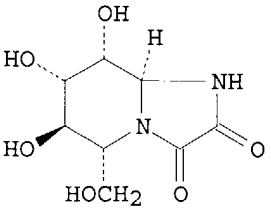


RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



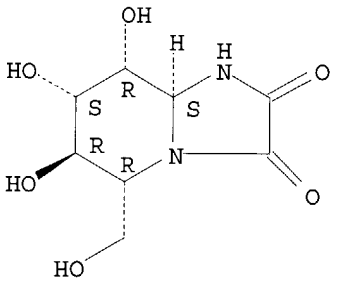
I

AB FR 900494 (I) or its salts (e.g. acetate, lactate, sulfate, nitrate, etc.) from Kitasatosporia kifunense number 9482 have therapeutic effects against autoimmune diseases including systemic lupus erythematosus, chronic rheumatism, and immune nephritis. Thus, in rats with exptl. arthritis induced by collagen, etc., I given orally or i.m. had anti-inflammatory effects.

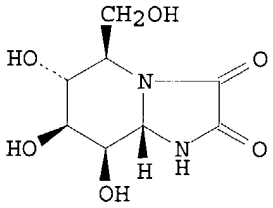
L4 ANSWER 33 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:533874 CAPLUS
DOCUMENT NUMBER: 111:133874
TITLE: Structure of kifunensine, a new immunomodulator isolated from an actinomycete

AUTHOR(S): Kayakiri, Hiroshi; Takase, Shigehiro; Shibata, Toshihiro; Okamoto, Masanori; Terano, Hiroshi; Hashimoto, Masashi; Tada, Toshiji; Koda, Shigetaka
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Journal of Organic Chemistry (1989), 54(17), 4015-16
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 111:133874
IT **109944-15-2**
RL: PRP (Properties)
(crystal and mol. structure of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



GI



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AB On the basis of chemical and phys. evidence and x-ray crystal anal., the structure of kifunensine, isolated from an actinomycete as an immunomodulator, has been determined to be I. I is unique in respect that it possesses an amino function at C-1 of a 1,5-iminopyranose (mannojirimycin) and exists as a stable cyclic oxamide derivative It is the 1st sample of this type of compds. found in nature.

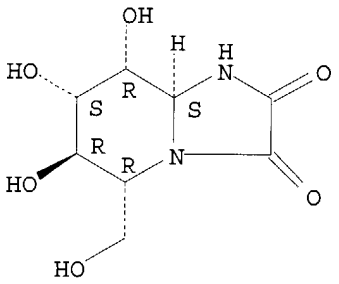
L4 ANSWER 34 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:634827 CAPLUS
DOCUMENT NUMBER: 107:234827
TITLE: Immunoregulator substance FR900494 manufacture with Kitassatosporia
INVENTOR(S): Ishimi, Morita; Nakayama, Osamu; Terano, Hiroshi; Kosaka, Masanobu
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.

CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62161796	A2	19870717	JP 1986-2793	19860108
JP 05071235	B4	19931006		
PRIORITY APPLN. INFO.:			JP 1986-2793	19860108

IT **109944-15-2P**, FR900494
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manufacture of, with Kitassatosporia kifunense)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

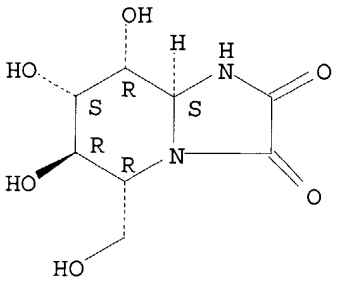


AB Immunoregulator substance FR900494 having a mol. weight of 232, a mol. formula of C8H12N2O6, and a m.p. (decomposition point) of 120-130° is manufactured with Kitassatosporia species. K. kifunense Number 9482 was cultured in a medium containing soluble starch, dry yeast, and soybean flour at 30° for 3 days. The culture filtrate was processed to obtain FR900494 as a white powder which decomposed at 120-130°.

L4 ANSWER 35 OF 35 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:493201 CAPLUS
DOCUMENT NUMBER: 107:93201
TITLE: A new immunomodulator, FR-900494: taxonomy, fermentation, isolation, and physicochemical and biological characteristics
AUTHOR(S): Iwami, Morita; Nakayama, Osamu; Terano, Hiroshi; Kohsaka, Masanobu; Aoki, Hatsuo; Imanaka, Hiroshi
CORPORATE SOURCE: Explor. Res. Lab., Fujisawa Pharm. Co., Ltd., Ibaraki, 300-26, Japan
SOURCE: Journal of Antibiotics (1987), 40(5), 612-22
CODEN: JANTAJ; ISSN: 0021-8820
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **109944-15-2**
RL: BIOL (Biological study)
(from Kitasatosporia kifunense, isolation and properties of)
RN 109944-15-2 CAPLUS
CN Imidazo[1,2-a]pyridine-2,3-dione, hexahydro-6,7,8-trihydroxy-5-

(hydroxymethyl)-, (5R,6R,7S,8R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB FR-900494 is a new type of immunoactive substance produced by an actinomycete, Kitasatosporia kifunense sp. nov. FR-900494 exhibits a competitive action against immunosuppressive factor produced in the serum of tumor-bearing mice and has the capacity to restore the depression of lymphocytes.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	175.39	331.44
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-25.73	-25.73

STN INTERNATIONAL LOGOFF AT 20:06:11 ON 02 AUG 2004